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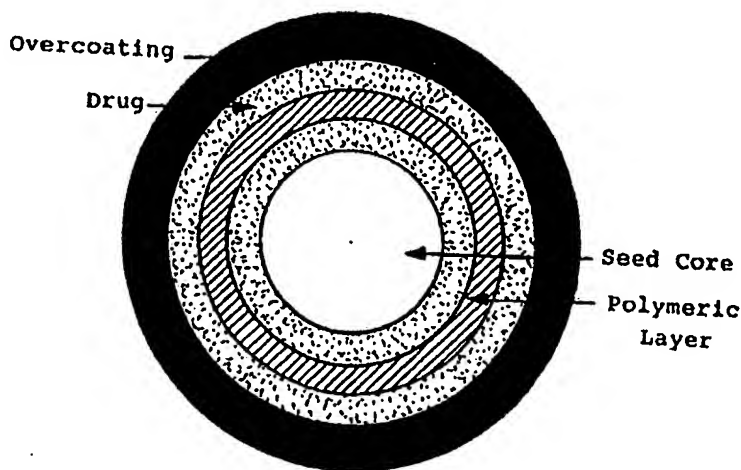
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(54) Title: ORAL PULSED DOSE DRUG DELIVERY SYSTEM



(57) Abstract

A multiple pulsed dose drug delivery system for pharmaceutically active amphetamine salts, comprising an immediate-release component and an enteric delayed-release component wherein (1) the enteric release coating has a defined minimum thickness; and/or (2) there is a protective layer between the pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating. The product can be composed of either one or a number of beads in a dosage form, including either capsule, tablet, or sachet method for administering the beads.

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## ORAL PULSED DOSE DRUG DELIVERY SYSTEM

This application is a continuation-in-part of U.S. Patent No. 6,322,819.

This invention pertains to a multiple unit dosage form delivery system comprising one or more amphetamine salts for administering the amphetamine salts to a recipient.

### Background of the Invention

Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems, compared to immediate release preparations. However, for certain drugs, sustained release delivery is not suitable and is affected by the following factors:

**First pass metabolism:** Some drugs, such as  $\beta$  blockers,  $\beta$ -estradiol, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

**Biological tolerance:** Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.

**Chronopharmacology and circadian rhythms:** Circadian rhythms in certain physiological functions are well established. It has been recognized that many

symptoms and onset of disease occur during specific time periods of the 24 hour day, *e.g.*, asthma and angina pectoris attacks are most frequently in the morning hours (1,2).

**Local therapeutic need:** For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

**Gastric irritation or drug instability in gastric fluid:** For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

**Drug absorption differences in various gastrointestinal segments:** In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feces.

Pulsed dose delivery systems, prepared as either single unit or multiple unit formulations, and which are capable of releasing the drug after a predetermined time, have been studied to address the aforementioned problematic areas for sustained release preparations. These same factors are also problematic in pulsed dose formulation development. For example, gastrointestinal transit times vary not only from patient to patient but also within patients as a result of food intake, stress, and illness; thus a single-unit pulsed-release system may give higher variability compared to a multiple unit system. Additionally, drug layering or core making for multiple unit systems is a time-consuming and hard-to-optimize process. Particularly challenging for formulation scientists has been overcoming two conflicting hurdles for pulsatile formulation development, *i.e.*, lag time and rapid release.

Various enteric materials, *e.g.*, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and the EUDRAGIT® acrylic polymers, have been used as gastroresistant, enterosoluble coatings for single drug pulse

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release in the intestine (3). The enteric materials, which are soluble at higher pH values, are frequently used for colon-specific delivery systems. Due to their pH-dependent attributes and the uncertainty of gastric retention time, *in-vivo* performance as well as inter- and intra-subject variability are major issues for using enteric coated systems as a time-controlled release of drugs.

A retarding swellable hydrophilic coating has been used for oral delayed release systems (4,5). It was demonstrated that lag time was linearly correlated with coating weight gain and drug release was pH independent.

Hydroxypropyl methylcellulose barriers with erodible and/or gellable characteristics formed using press coating technology for tablet dosage forms have been described to achieve time-programmed release of drugs (6). Barrier formulation variables, such as grade of hydroxypropyl methylcellulose, water-soluble and water-insoluble excipients, significantly altered the lag time and the release rate from the center cores.

Special grades of hydroxypropyl methylcellulose, *e.g.*, METOLOSE® 60SH, 90SH (Shin-Etsu Ltd., Japan), and METHOCEL® F4M (Dow Chemical Company, USA), as a hydrophilic matrix material have been used to achieve bimodal drug release for several drugs, *i.e.*, aspirin, ibuprofen, and adinazolam (7). Bimodal release is characterized by a rapid initial release, followed by a period of constant release, and finalized by a second rapid drug release.

Tablets or capsules coated with a hydrophobic wax-surfactant layer, made from an aqueous dispersion of carnauba wax, beeswax, polyoxyethylene sorbitan monooleate, and hydroxypropyl methylcellulose have been used for rapid drug release after a predetermined lag time. For example,. However, even though a two-hour lag time was achieved for the model drug theophylline at a higher coating level (60%), three hours were required for a complete release of theophylline after the lag time. (8)

A sustained-release drug delivery system is described in U.S. Patent No. 4,871,549. When this system is placed into dissolution medium or the gastrointestinal tract, water influx and the volume expansion of the swelling agent cause the explosion of the water permeable membrane. The drug thus releases after a predetermined time period.

The OROS® push-pull system (Alza Company) has been developed for pulsatile delivery of water-soluble and water-insoluble drugs (9, 10), e.g. the OROS-CT® system and is based on the swelling properties of an osmotic core compartment which provides a pH-independent, time-controlled drug release.

The PULSINCAP® dosage form releases its drug content at either a predetermined time or at a specific site (e.g., colon) in the gastrointestinal tract (11). The drug formulation is contained within a water-insoluble capsule body and is sealed with a hydrogel plug. Upon oral administration, the capsule cap dissolves in the gastric juice and the hydrogel plug swells. At a controlled and predetermined time point, the swollen plug is ejected from the PULSINCAP® dosage form and the encapsulated drug is released. A pulsatile capsule system containing captopril with release after a nominal 5-hr period was found to perform reproducibly in dissolution and gamma scintigraphy studies. However, in the majority of subjects, no measurable amounts of the drug were observed in the blood, possibly due to instability of the drug in the distal intestine. (12)

ADDERAL® comprises a mixture of four amphetamine salts which, in combination, is indicated for treatment of Attention Deficit Hyperactivity Disorder in children from 3-10 years of age. One disadvantage of current treatment is that a tablet form is commonly used which many young children have difficulty in swallowing. Another disadvantage of current treatment is that two separate doses are administered, one in the morning and one approximately 4-6 hours later, commonly away from home under other than parental supervision. This current form of treatment, therefore, requires a second treatment which is time-consuming, inconvenient and may be problematic for those children having difficulties in swallowing tablet formulations.

#### SUMMARY OF THE INVENTION

Accordingly, in view of a need for successfully administering a multiple unit pulsed dose of amphetamine salts and mixtures thereof, the present invention provides an oral multiple unit pulsed dose delivery system for amphetamine salts and mixtures thereof. Figure 1 illustrates the desired target plasma level profile of the pharmaceutical active contained within the delivery system.

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According to a further aspect of the present invention, there is provided a pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising: (a) one or more  
5 pharmaceutically active amphetamine salts covered with an immediate release coating; and (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating  
10 releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release.

According to yet a further aspect of the present  
15 invention, there is provided a pharmaceutical composition for delivery of at least one amphetamine salt, comprising: (a) at least one pharmaceutically active amphetamine salt covered with an immediate release coating; and (b) at least one pharmaceutically active amphetamine salt covered with an  
20 enteric release coating, said component (a) providing for an immediate release of amphetamine salt to provide a first blood level of amphetamine salt and component (b) providing a delayed pulsed enteric release of amphetamine salt that increases the blood level of amphetamine salt to a second  
25 level that is greater than the first level provided by component (a), wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed  
30 enteric release.

According to still a further aspect of the present invention, there is provided a pharmaceutical composition

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for delivering one or more pharmaceutically active amphetamine salts comprising: (a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating; (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and (c) a protective layer over the enteric release coating.

According to another aspect of the present invention, there is provided a pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts comprising: (a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating; (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and (c) a protective layer between the one or more pharmaceutically active amphetamine salts and the enteric release coating.

According to yet another aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising: (a) an immediate release dosage form containing an amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and (b) a

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delayed release dosage form containing an amount effective to treat ADHD in a human patient of one or more amphetamine base salts, wherein said amphetamine base salts are released from the delayed release dosage form beginning 2-6 hours  
5 after administration, after which release the maximum plasma concentration of the amphetamine base salts reaches a level greater than any previous level reached after the beginning of said immediate release, and wherein said composition is sufficient to maintain an effective level of amphetamine  
10 base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

According to yet a further aspect of the present invention, there is provided an oral pharmaceutical  
15 composition for delivery of one or more amphetamine base salts comprising an immediate release dosage form containing a dosage amount of said one or more salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient, and a second dosage form containing a dosage amount  
20 of said one or more salts effective to treat ADHD in a human patient which has a release onset lag time sufficient that the plasma concentration/time profile of said composition is substantially the same as that of Figure 7, adjusted proportionally for said dosage amounts.

25 According to still a further aspect of the present invention, there is provided an oral pharmaceutical composition for delivery of one or more amphetamine base salts comprising an immediate release dosage form containing a dosage amount of said one or more salts effective to treat  
30 Attention Deficit Hyperactivity Disorder (ADHD) in a human patient, and a second dosage form containing a dosage amount of said one or more salts effective to treat ADHD in a human



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patient which has a release onset lag time sufficient that the plasma concentration/time curve of said composition has substantially the same shape of that of Figure 7, adjusted proportionally for said dosage amounts.

5           According to another aspect of the present invention, there is provided an oral pharmaceutical composition for delivery of dosage amounts of one or more amphetamine base salts sufficient to provide an Attention Deficit Hyperactivity Disorder (ADHD) effective plasma level  
10 in said patient for at least 8 hours without further administration of amphetamine base salts and which has a plasma concentration/time curve which is substantially the same as that of Figure 7, adjusted proportionally for said dosage amounts.

15           According to yet another aspect of the present invention, there is provided an oral pharmaceutical composition for delivery of one or more amphetamine base salts comprising an immediate release dosage form containing a dosage amount of said one or more salts effective to treat  
20 Attention Deficit Hyperactivity Disorder (ADHD) in a human patient, and a second dosage form containing a dosage amount of said one or more salts effective to treat ADHD in a human patient, wherein the plasma concentration/time profile of said composition is substantially the same as that of Figure  
25 7, adjusted proportionally for said dosage amounts.

          According to another aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising: (a) an immediate release dosage form containing a first dosage amount of one  
30 or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient;

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and (b) a delayed release dosage form containing a second dosage amount effective to treat ADHD in a human patient of one or more amphetamine base salts, wherein said amphetamine base salts are released from the delayed release dosage form beginning at a time after administration such that the maximum plasma concentration of the amphetamine base salts reaches a level greater than any previous level reached after the beginning of said immediate release, and wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

According to still another aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising: (a) an immediate release dosage form containing a first dosage amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and (b) a delayed release dosage form containing a second dosage amount effective to treat ADHD in a human patient of one or more amphetamine base salts, wherein said amphetamine base salts are released from the delayed release dosage form beginning at a time after administration such that the maximum plasma concentration of amphetamine is reached about 7 hours after administration, wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

According to a further aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising: (a) an immediate

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release dosage form containing an amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and (b) a delayed release dosage form containing an amount effective to treat ADHD in a human patient of one or more amphetamine base salts, wherein said salts are a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, wherein said amphetamine base salts are released from the delayed release dosage form beginning at a time after administration such that the maximum plasma concentration of dextro-salts in said mixture is about 40 ng/ml for about a 10 mg dose in each of said dosage forms, or a concentration proportional thereto for a dose in each of said dosage forms other than about 10 mg, and wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

According to yet a further aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising amphetamine base salts, which has substantially the same mean plasma concentration profile as an orally administrable pharmaceutical composition comprising: (a) an immediate release dosage form containing an amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient coated onto a particulate core; and (b) a delayed release dosage form containing substantially the same amount effective to treat ADHD in a human patient of one or more amphetamine base salts, coated onto a particulate core and having thereon a pH-dependent enteric coating comprising a copolymer of

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methacrylic acid and methacrylic acid methyl ester, wherein said salts are a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, wherein essentially all  
5 of said amphetamine base salts are released from the delayed release dosage form within about 60 minutes after initiation of said delayed release, beginning at a time after administration such that the maximum plasma concentration of the amphetamine base salts reaches a level greater than any  
10 previous level reached after the beginning of said immediate release, and wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts, said composition  
15 having said substantially the same mean plasma concentration profile.

According to still a further aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising: (a) an immediate  
20 release dosage form containing an amount of a mixture of amphetamine base salts effective to treat ADHD in a human patient; and (b) a delayed release dosage form containing an amount effective to treat ADHD in a human patient of a mixture of amphetamine base salts, wherein said delayed  
25 release dosage form comprises amphetamine base salts coated with a pH-dependent enteric matrix or coating of a thickness of equal to or greater than about 20  $\mu\text{m}$ , and wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at  
30 least 8 hours without further administration of amphetamine base salts.

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According to another aspect of the present invention, there is provided an orally administrable pharmaceutical composition comprising: (a) an immediate release dosage form containing an amount of a mixture of amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and (b) a delayed release dosage form containing an amount effective to treat ADHD in a human patient of a mixture of amphetamine base salts, wherein said mixture of amphetamine base salts comprises dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, wherein said delayed release dosage form comprises amphetamine base salts coated with a pH-dependent enteric matrix or coating of a thickness of equal to or greater than about 20  $\mu\text{m}$ , wherein said pH-dependent matrix or coating comprises copolymerized methacrylic acid/methacrylic acid methyl ester, and wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

According to yet another aspect of the present invention, there is provided a dosage form for once a day administration of one or more amphetamine base salts, produced by a process comprising, coating first particulate cores with said amphetamine base salts to provide immediate release of said salts upon administration, coating second particulate cores with one or more amphetamine base salts and then coating the resultant amphetamine base salts coated cores with an enteric coating effective to delay the onset of release of said amphetamine base salts such that the maximum plasma concentration of the amphetamine base salts reaches a level greater than any previous level reached

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after the beginning of said immediate release, drying said coated cores, and filling a dosage form with a sufficient amount of each of said first and second coated cores such that said dosage form is sufficient to maintain an effective  
5 level of amphetamine base salts in a patient over the course of at least 8 hours without further administration of amphetamine base salts.

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In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts that includes:

(a) one or more pharmaceutically active amphetamine salts that are covered with an immediate release coating, and

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

In one embodiment, the immediate release and enteric release portions of the composition are present on the same core.

In another embodiment, the immediate release and enteric release components are present on different cores.

It is also contemplated that the composition may include a combination of the hereinabove referred to cores (one or more cores that include both components on the same core and one or more cores that include only one of the two components on the core).

The present invention provides a composition in which there is immediate release of drug and enteric release of drug wherein the enteric release is a pulsed release and wherein the drug includes one or more amphetamine salts and mixtures thereof.

The immediate release component releases the pharmaceutical agent in a pulsed dose upon oral administration of the delivery system.

The enteric release coating layer retards or delays the release of the pharmaceutical active or drug for a specified time period ("lag time") until a predetermined time, at which time the release of the drug is rapid and complete, *i.e.*, the entire dose is released within about 30-60 minutes under predetermined environmental conditions, *i.e.* a particular location within the gastrointestinal tract.

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The delay or lag time will take into consideration factors such as transit times, food effects, inflammatory bowel disease, use of antacids or other medicaments which alter the pH of the GI tract.

In a preferred embodiment, the lag time period is only time-dependent, *i.e.*, pH independent. The lag time is preferably within 4 to 6 hours after oral administration of the delivery system.

In one aspect, the present invention is directed to a composition that provides for enteric release of at least one pharmaceutically active amphetamine salt, including at least one pharmaceutically active amphetamine salt that is coated with an enteric coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

In attempting to provide for enteric release of an amphetamine salt, applicants found that use of an enteric release coating as generally practiced in the art did not provide effective enteric release.

Typical enteric coating levels did not meet the above requirements for the desired dosage profile of amphetamine salts. Using the typical amount of enteric coating (10-20 $\mu$ ) resulted in undesired premature leakage of the drug from the delivery system into the upper gastrointestinal tract and thus no drug delivery at the desired location in the gastrointestinal tract after the appropriate lag time. Thus this coating did not meet the requirements for the drug release profile to provide full beneficial therapeutic activity at the desired time.

Surprisingly, applicants found that using a thicker application of enteric coating on the formulation allowed for the second pulsed dose to be released only and completely at the appropriate time in the desired predetermined area of the gastrointestinal tract, *i.e.*, in the intestine.

This was surprising because an increase in thickness of about 5-10 $\mu$  of enteric coatings above a minimum thickness of about 10-20 $\mu$  typically does not have a significant



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effect on release of drug from within such coatings. Enteric coatings typically are pH dependent and will only dissolve/disperse when exposed to the appropriate environment. Typically, application of a thicker coating (greater than 20 $\mu$ ) will only marginally increase the time for complete release at the appropriate environmental condition i.e., for a brief period of time (20 minutes). Using the typical coating, applicants could not achieve the desired result - rather, the coating leaked before the predetermined time in an inappropriate environment resulting in significant loss of the therapeutic agent.

Accordingly, in one aspect, the pulsed enteric release of the amphetamine salts is accomplished by employing a certain minimum thickness of the enteric coating.

In one embodiment of the invention, the pulsed dose delivery comprises a composition which comprises one or more pharmaceutically active amphetamine salts; an enteric coating over the one or more pharmaceutically active amphetamine salts, wherein the thickness of the enteric coating layer is at least 25 $\mu$ ; a further layer of one or more pharmaceutically active amphetamine salts over the enteric coating layer; and an immediate release layer coating. The thicker enteric coating surprisingly provides the required delayed immediate release of the pharmaceutically active amphetamine salt at the desired time in the desired area of the gastrointestinal tract. Figure 2 illustrates a model of this delivery system.

In this aspect, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed around which the enteric coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

It has further been discovered that a delayed immediate release drug delivery can also be accomplished by coating the drug first with a protective layer prior to applying the enteric coating.

Thus, in another embodiment, the pulsed enteric release is accomplished by employing a protective layer between the drug and the enteric coating. When using a protective coating, the enteric coating may be of an increased thickness or may be of lower thickness.

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Thus, in another aspect, the object of the invention is met by providing a composition comprising one or more pharmaceutically active amphetamine salts; a protective layer coating over the one or more pharmaceutically active amphetamine salt layer(s), and an enteric coating layer over the protective coating layer; a further pharmaceutically active amphetamine salt layer and an immediate release layer coating. In a preferred embodiment of this aspect, the thickness of the enteric coating is at least 25 $\mu$ , and the protective layer comprises an immediate release coating.

With respect to this embodiment of the invention, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed, during the core seed manufacturing process, around which the protective coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

In another embodiment, the pulsed enteric release is accomplished by employing a protective layer over the enteric coating.

Accordingly, in this embodiment of the present invention, there is provided a pulsed dose release drug delivery system comprising one or more pharmaceutically active amphetamine salts; an enteric coating layer over the pharmaceutically active amphetamine salt layer(s); and a protective layer over the enteric coating; a second pharmaceutically active amphetamine salt layer; and an immediate release layer coating.

In one aspect of this embodiment, the protective layer is comprised of one or more components, which includes an immediate release layer and a modifying layer. The modifying layer is preferably comprised of a semi water-permeable polymer. Applicants have surprisingly found that a semi-permeable polymer coating used in combination with an immediate release layer coating provided a delayed pulsed release drug delivery profile when layered over the enteric coating.

Thus, in this embodiment, the protective layer comprises a semi-permeable polymer and an immediate release coating layer. In a preferred embodiment, the modifying layer comprises a first layer of a semi-permeable polymer which is adjacent to the enteric coating

layer and a second coating layer over the semi-permeable polymer coating layer comprising an immediate release polymer coating layer.

In one aspect of this embodiment, a semi-permeable polymer, which may comprise a low water-permeable pH-insensitive polymer, is layered onto the outer surface of the enteric layer, in order to obtain prolonged delayed release time. This semi-permeable polymer coating controls the erosion of the pH-sensitive enteric polymer in an alkaline pH environment in which a pH-sensitive polymer will dissolve rapidly. Another pH-sensitive layer may be applied onto the surface of a low water-permeability layer to further delay the release time.

In a still further aspect of the invention, in addition to a protective layer, the composition comprises an acid which is incorporated into the pharmaceutical active layer or coated onto the surface of the active layer to reduce the pH value of the environment around the enteric polymer layer. The acid layer may also be applied on the outer layer of the pH-sensitive enteric polymer layer, followed by a layer of low water-permeability polymer. The release of the active thus may be delayed and the dissolution rate may be increased in an alkaline environment.

In a further embodiment, the protective coating may be used both over the drug and over the enteric coating.

With respect to this embodiment of the invention, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed, during the core seed manufacturing process, around which the enteric coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

The drug delivery system of the present invention as described herein preferably comprises one or a number of beads or beadlets in a dosage form, either capsule, tablet, sachet or other method of orally administering the beads.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

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Figure 1 illustrates a multiple pulse drug delivery system target plasma profile of the drug delivery system of the present invention. The profile reflects an immediate-release component followed by a delayed-release component.

Figure 2 schematically illustrates the delayed-release system of the present invention.

Figure 2a graphically illustrates a pulsed dose delivery system.

Figures 2b and c graphically illustrate the drug release mechanism from the proposed delivery system.

Figure 3 is a plot of the percent drug released versus time from the drug-loaded pellets described in Example 1 which exemplifies the immediate release component of the present invention.

Figure 4 is a plot of the percent drug released versus time from the coated pellets described in Example 2 which exemplifies the immediate release component and the delayed release components of the present invention.

Figure 5 is a plot of the percent drug released versus time from the coated pellets of Example 3 which exemplifies the immediate release component and the delayed release components of the present invention.

Figure 6 illustrates the drug release profile of coated pellets described in Example 4 which exemplifies the immediate release component and the delayed release components of the present invention.

Figure 7 is a plot of a profile of plasma amphetamine concentration after administration of a composite capsule containing the immediate release pellets and delayed release pellets from Examples 1 and 2, respectively.

Figure 8 is a plot of a profile of plasma amphetamine concentration after administration of a composite capsule containing the immediate release pellets and delayed release pellets from Examples 1 and 3, respectively.

#### DETAILED DESCRIPTION OF THE INVENTION

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The present invention comprises a core or starting seed, either prepared or commercially available product. The cores or starting seeds can be sugar spheres; spheres made from microcrystalline cellulose and any suitable drug crystals.

The materials that can be employed in making drug-containing pellets are any of those commonly used in pharmaceuticals and should be selected on the basis of compatibility with the active drug and the physicochemical properties of the pellets. The additives except active drugs are chosen below as examples:

Binders such as cellulose derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer and the like.

Disintegration agents such as corn starch, pregelatinized starch, cross-linked carboxymethylcellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®), cross-linked polyvinylpyrrolidone (PLASDONE XL®), and any disintegration agents used in tablet preparations.

Filling agents such as lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

Surfactants such as sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, bile salts, glyceryl monostearate, PLURONIC® line (BASF), and the like.

Solubilizers such as citric acid, succinic acid, fumaric acid, malic acid, tartaric acid, maleic acid, glutaric acid sodium bicarbonate and sodium carbonate and the like.

Stabilizers such as any antioxidation agents, buffers, acids, and the like, can also be utilized.

Methods of manufacturing the core include

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a. **Extrusion-Spheronization** - Drug(s) and other additives are granulated by addition of a binder solution. The wet mass is passed through an extruder equipped with a certain size screen. The extrudates are spheronized in a marumerizer. The resulting pellets are dried and sieved for further applications.

b. **High-Shear Granulation** - Drug(s) and other additives are dry-mixed and then the mixture is wetted by addition of a binder solution in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

c. **Solution or Suspension Layering** - A drug solution or dispersion with or without a binder is sprayed onto starting seeds with a certain particle size in a fluid bed processor or other suitable equipment. The drug thus is coated on the surface of the starting seeds. The drug-loaded pellets are dried for further applications.

For purposes of the present invention, the core particles have a diameter in the range of about 50-1500 microns; preferably 100-800 microns.

These particles can then be coated in a fluidized bed apparatus with an alternating sequence of coating layers.

The core may be coated directly with a layer or layers of at least one pharmaceutically active amphetamine salts and/or the pharmaceutically active amphetamine salt may be incorporated into the core material. Pharmaceutical active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base, all chemical and chiral derivatives and salts thereof; methylphenidate, all chemical and chiral derivatives and salts thereof; phenylpropanolamine and its salts; and all other compounds indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

A protective layer may be added on top of the pharmaceutical active containing layer and also may be provided between active layers. A separation or protective layer may be added onto the surface of the active-loaded core, and then the enteric layer is coated thereupon. Another active layer may also be added to the enteric layer to deliver an initial dose.

A protective coating layer may be applied immediately outside the core, either a drug-containing core or a drug-layered core, by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. Suitable materials for the protective layer include cellulose derivatives such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, ethyl cellulose aqueous dispersions (AQUACOAT®, SURELEASE®), EUDRAGIT® RL 30D, OPADRY® and the like. The suggested coating levels are from 1 to 6%, preferably 2-4 % (w/w).

The enteric coating layer is applied onto the cores with or without seal coating by conventional coating techniques, such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. All commercially available pH-sensitive polymers are included. The pharmaceutical active is not released in the acidic stomach environment of approximately below pH 4.5, but not limited to this value. The pharmaceutical active should become available when the pH-sensitive layer dissolves at the greater pH; after a certain delayed time; or after the unit passes through the stomach. The preferred delay time is in the range of two to six hours.

Enteric polymers include cellulose acetate phthalate, Cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, materials known under the trade name EUDRAGIT® L12.5, L100, or EUDRAGIT® S12.5, S100 or similar compounds used to obtain enteric coatings. Aqueous colloidal polymer dispersions or re-dispersions can be also applied, e.g. EUDRAGIT® L 30D-55, EUDRAGIT® L100-55, EUDRAGIT® S100, EUDRAGIT® preparation 4110D (Rohm Pharma); AQUATERIC®, AQUACOAT® CPD 30 (FMC); KOLLICOAT MAE® 30D and 30DP (BASF); EASTACRYL® 30D (Eastman Chemical).

The enteric polymers used in this invention can be modified by mixing with other known coating products that are not pH sensitive. Examples of such coating products include the neutral methacrylic acid esters with a small portion of trimethylammonioethyl methacrylate chloride, sold currently under the trade names EUDRAGIT® RS and

EUDRAGIT® RL; a neutral ester dispersion without any functional groups, sold under the trade names EUDRAGIT® NE30D; and other pH independent coating products.

The modifying component of the protective layer used over the enteric coating can include a water penetration barrier layer (semipermeable polymer) which can be successively coated after the enteric coating to reduce the water penetration rate through the enteric coating layer and thus increase the lag time of the drug release. Sustained-release coatings commonly known to one skilled in the art can be used for this purpose by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. For example, the following materials can be used, but not limited to: Cellulose acetate, Cellulose acetate butyrate, Cellulose acetate propionate, Ethyl cellulose, Fatty acids and their esters, Waxes, zein, and aqueous polymer dispersions such as EUDRAGIT® RS and RL 30D, EUDRAGIT® NE 30D, AQUACOAT®, SURELEASE®, cellulose acetate latex. The combination of above polymers and hydrophilic polymers such as Hydroxyethyl cellulose, Hydroxypropyl cellulose (KLUCEL®, Hercules Corp.), Hydroxypropyl methylcellulose (METHOCEL®, Dow Chemical Corp.), Polyvinylpyrrolidone can also be used.

An overcoating layer can further optionally be applied to the composition of the present invention. OPADRY®, OPADRY II® (Colorcon) and corresponding color and colorless grades from Colorcon can be used to protect the pellets from being tacky and provide colors to the product. The suggested levels of protective or color coating are from 1 to 6%, preferably 2-3 % (w/w).

Many ingredients can be incorporated into the overcoating formula, for example to provide a quicker immediate release, such as plasticizers: acetyltriethyl citrate, triethyl citrate, acetyltributyl citrate, dibutylsebacate, triacetin, polyethylene glycols, propylene glycol and the others; lubricants: talc, colloidal silica dioxide, magnesium stearate, calcium stearate, titanium dioxide, magnesium silicate, and the like.

The composition, preferably in beadlet form, can be incorporated into hard gelatin capsules, either with additional excipients, or alone. Typical excipients to be added to a capsule formulation include, but are not limited to: fillers such as microcrystalline cellulose,



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soy polysaccharides, calcium phosphate dihydrate, calcium sulfate, lactose, sucrose, sorbitol, or any other inert filler. In addition, there can be flow aids such as fumed silicon dioxide, silica gel, magnesium stearate, calcium stearate or any other material imparting flow to powders. A lubricant can further be added if necessary by using polyethylene glycol, leucine, glyceryl behenate, magnesium stearate or calcium stearate.

The composition may also be incorporated into a tablet, in particular by incorporation into a tablet matrix, which rapidly disperses the particles after ingestion. In order to incorporate these particles into such a tablet, a filler/binder must be added to a table that can accept the particles, but will not allow their destruction during the tableting process. Materials that are suitable for this purpose include, but are not limited to, microcrystalline cellulose (AVICEL®), soy polysaccharide (EMCOSOY®), pre-gelatinized starches (STARCH® 1500, NATIONAL® 1551), and polyethylene glycols (CARBOWAX®). The materials should be present in the range of 5-75% (w/w), with a preferred range of 25-50% (w/w).

In addition, disintegrants are added in order to disperse the beads once the tablet is ingested. Suitable disintegrants include, but are not limited to: cross-linked sodium carboxymethyl cellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®, PRIMOJEL®), and cross-linked polyvinylpyrrolidone (Plasone-XL). These materials should be present in the rate of 3-15% (w/w), with a preferred range of 5-10% (w/w).

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, and hydrogenated vegetable oil. These lubricants should be present in amounts from 0.1-10% (w/w), with a preferred range of 0.3-3.0% (w/w).

Tablets are formed, for example, as follows. The particles are introduced into a blender along with AVICEL®, disintegrants and lubricant, mixed for a set number of minutes to provide a homogeneous blend which is then put in the hopper of a tablet press with which tablets are compressed. The compression force used is adequate to form a tablet; however, not sufficient to fracture the beads or coatings.

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It will be appreciated that the multiple dosage form of the present invention can deliver rapid and complete dosages of pharmaceutically active amphetamine salts to achieve the desired levels of the drug in a recipient over the course of about 8 hours with a single oral administration.

In so doing, the levels of drug in blood plasma of the pharmaceutically active amphetamine salts will reach a peak fairly rapidly after about 2 hours, and after about 4 hours a second pulse dose is released, wherein a second fairly rapid additive increase of plasma drug levels occurs which slowly decreases over the course of the next 12 hours.

The following examples are presented to illustrate and do not limit the invention.

### EXAMPLES

#### Example 1

##### Immediate release formulation

The following formulation was used to layer the drug onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg were put into a FLM-15 fluid bed processor with a 9" Wurster column and fluidized at 60 °C. The suspension of mixed amphetamine salts (MAS) with 1% HPMC E5 Premium (Dow Chemical) as a binder was sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines were observed with a yield of at least 98%. The drug-loaded cores were used to test enteric coatings and sustained release coatings.

Table 1

Ingredients	Amount (%)
Nonpareil seed	88.00
mixed amphetamine salts	11.40
METHOCEL® E5 Premium	0.60
Water	*

\*removed during processing

The drug release profile of the drug-loaded pellets of this example is shown in Figure

3.

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**Example 2**

The following formulation was used to coat the mixed amphetamine salts loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55 (Rohm Pharma, Germany) coating dispersion. 2 kg of MASL pellets were loaded into a fluid bed processor with a reduced Wurster column equipped with a precision coater (MP 2/3, Niro Inc.). The coating dispersion was prepared by dispersing Triethyl citrate, Talc and EUDRAGIT® L 30D-55 into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized MASL pellets. The spraying was continued until the targeted coating level was achieved (20 $\mu$ ). The coated pellets were dried at 30-35 °C for 5 minutes before stopping the process. The enteric coated PPA pellets were tested at different pH buffers by a USP paddle method. The drug content was analyzed using HPLC. The results showed that the enteric coating delayed the drug release from the coated pellets until after exposure to pH 6 or higher (see Table 2 below). (Reference # AR98125-4)

**Table 2**

<b>Ingredients</b>	<b>Amount (%)</b>
MASL pellets	40.00
EUDRAGIT® L 30D-55	24.88
Triethyl citrate	2.52
Talc	2.60
Water	*

\*removed during processing

The drug release profile of the coated pellets of this example is shown in Figure 4.

**Example 3**

The following formulation was used to coat the MASL pellets from Example 1 with the EUDRAGIT® 4110D (Rohm Pharma, Germany) coating dispersion. MASL pellets (2 kg) were loaded in a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by dispersing Triethyl citrate, Talc and EUDRAGIT® 4110D into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized MASL pellets. The spraying was continued until the targeted coating level was achieved. The coated pellets were dried at 30-35 °C for 5 minutes before stopping the process. The enteric coated MASL pellets were tested using a USP paddle method at different pH buffers. The drug content was analyzed using HPLC. The enteric coating delayed the drug release for several hours from the coated

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pellets until the pH value reached 6.8 or higher, as shown below in Table 3. (Reference # AR98I25-3)

Table 3

Ingredients	Amount (%)
MASL pellets	70.00
Eudragit® 4110D	26.24
Triethyl citrate	0.76
Talc	3.00
Water	*

\*removed during processing

The drug release profile of coated pellets of this example is shown in Figure 5.

#### Example 4

The following formulation was selected to coat the enteric coated MASL pellets. Coated MASL pellets from Example 2 or coated MASL pellets from Example 3 (2 kg of either) were loaded into a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water for at least 15 minutes prior to spraying. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized pellets. The spraying was continued until the targeted coating level was achieved. The coated pellets were coated with a thin layer of OPADRY® white (Colorcon) (2%) to prevent the tackiness of the coated pellets during storage. The coated pellets were then dried at 35-40 °C for 10 minutes before discharging from the bed. The drug dissolution from both coated pellets was performed using a USP paddle method at different pH buffers. The drug content was analyzed using HPLC. The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release up to 2 hours after the buffer switched from pH 1 to pH 7.5. (Reference ## AR98I25-1)

Table 4

Ingredients	Amount (%)
Enteric coated MASL pellets	90.00
SURELEASE®	8.00
OPADRY® white	2.00
Water	*

\*removed during processing

The drug release profile of the coated pellets from this example is shown in Figure 6.

#### Example 5

A pulsatile delivery system can be achieved by combining the immediate release pellets (Example 1) with delayed release pellets (Example 2 or Example 3). The immediate-release pellets equivalent to half the dose and the delayed-release pellets equivalent to half the dose are filled into a hard gelatin capsule to produce the oral pulsed dose delivery system. The delayed-release portion releases the amphetamine salts rapidly and completely, after a specified lag time. The capsule products containing immediate-release pellets and delayed-release pellets (Example 1 plus Example 2 and Example 1 plus Example 3) were tested in a crossover human study. Figures 7 and 8 show the typical profiles of plasma amphetamine concentration after administration of a composite capsule containing the immediate-release pellets and delayed-release pellets from Examples 1 and 2 (10mg dose each pellet type) and a capsule containing the pellets from immediate-release pellets and delayed-release pellets from Examples 1 and 3 (10mg dose each pellet type), respectively. The general plasma profiles are similar to the desired target plasma level profile shown in Figure 1.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

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CLAIMS:

1. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:

5 (a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating; and

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release  
10 coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric  
15 release.

2. A pharmaceutical composition for delivery of at least one amphetamine salt, comprising:

(a) at least one pharmaceutically active amphetamine salt covered with an immediate release coating;  
20 and

(b) at least one pharmaceutically active amphetamine salt covered with an enteric release coating, said component (a) providing for an immediate release of amphetamine salt to provide a first blood level of  
25 amphetamine salt and component (b) providing a delayed pulsed enteric release of amphetamine salt that increases the blood level of amphetamine salt to a second level that is greater than the first level provided by component (a), wherein said enteric release coating releases essentially  
30 all of said one or more pharmaceutically active amphetamine



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salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release.

3. A pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts comprising:

(a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating;

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and

(c) a protective layer over the enteric release coating.

4. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts comprising:

(a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating;

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and

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(c) a protective layer between the one or more pharmaceutically active amphetamine salts and the enteric release coating.

5. The pharmaceutical composition of any one of  
5 claims 1 to 4, wherein said enteric release coating has a thickness of at least 25  $\mu$ .

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the one or more pharmaceutically active amphetamine salts are coated onto a core.

10 7. The pharmaceutical composition of any one of claims 1 to 5, wherein the one or more pharmaceutically active amphetamine salts are incorporated into a core.

8. The pharmaceutical composition of any one of claims 1 to 7, wherein the one or more pharmaceutically  
15 active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on a single core.

9. The pharmaceutical composition of any one of  
20 claims 1 to 7, wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on different cores.

25 10. The pharmaceutical composition of any one of claims 1 to 9, wherein said enteric release coating is a non-pH-dependent enteric release coating.

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11. The pharmaceutical composition of any one of claims 1 to 9, wherein said enteric release coating is a pH-dependent coating.

12. The pharmaceutical composition of any one of  
5 claims 1 to 11, wherein the delayed pulsed enteric release is from 4 to 6 hours after administration of the pharmaceutical composition.

13. The pharmaceutical composition of any one of  
10 claims 1 to 11, wherein the delayed pulsed enteric release releases the amphetamine salt in about 30 to 60 minutes after initiation of the release.

14. An orally administrable pharmaceutical composition comprising:

(a) an immediate release dosage form containing a  
15 first dosage amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and

(b) a delayed release dosage form containing a  
20 second dosage amount effective to treat ADHD in a human patient of one or more amphetamine base salts,

wherein said amphetamine base salts are released from the delayed release dosage form beginning 2-6 hours after administration, after which release the maximum plasma concentration of the amphetamine base salts reaches a level  
25 greater than any previous level reached after the beginning of said immediate release, and

wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient

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over the course of at least 8 hours without further administration of amphetamine base salts.

15. The composition of claim 14, wherein said first and second dosage amounts are substantially equal.

5 16. The composition of claim 14 or 15, wherein the composition includes an amount of amphetamine base salts to provide an effective level thereof in said patient without further administration over a course of twelve hours.

10 17. The composition of any one of claims 14 to 16 in the form of a capsule, said capsule including the immediate release dosage form and the delayed release dosage form.

18. The composition of any one of claims 14 to 17, wherein said delayed release dosage form is released about 3 to about 5 hours after administration.

15 19. The composition of any one of claims 14 to 17, wherein said delayed release dosage form is released about 3 to about 4 hours after administration.

20 20. The composition of any one of claims 14 to 17, wherein said delayed release dosage form is released about 4 hours after administration.

21. The composition of any one of claims 14 to 20, wherein the delayed release dosage form comprises a pH-dependent coating.

25 22. An oral pharmaceutical composition for delivery of one or more amphetamine base salts comprising an immediate release dosage form containing a first dosage amount of said one or more salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient, and a

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second dosage form containing a second dosage amount of said one or more salts effective to treat ADHD in a human patient which has a release onset lag time sufficient that the plasma concentration/time curve of said composition has  
5 substantially the same shape as that of Figure 7, adjusted proportionally for said first and second dosage amounts.

23. The pharmaceutical composition of claim 22, wherein said release onset lag time is about 2 to about 6 hours.

10 24. The pharmaceutical composition of claim 22, wherein said release onset lag time is about 3 to about 5 hours.

25. The pharmaceutical composition of claim 22, wherein said release onset lag time is about 3 to about 4  
15 hours.

26. The pharmaceutical composition of claim 22, wherein said release onset lag time is about 4 hours after administration.

27. The pharmaceutical composition of any one of  
20 claims 22 to 26, wherein said second dosage form comprises an enteric matrix or coating.

28. The pharmaceutical composition of any one of claims 22 to 26, wherein the second dosage form comprises a pH-dependent coating.

25 29. The pharmaceutical composition of any one of claims 22 to 28, wherein said second dosage form comprises an enteric coating having a thickness of 10-20 $\mu$ m.

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30. The pharmaceutical composition of any one claims 22 to 28, wherein the second dosage form comprises an enteric coating having a thickness of at least 25µm.

31. An oral pharmaceutical composition for delivery of  
5 dosage amounts of one or more amphetamine base salts  
sufficient to provide an Attention Deficit Hyperactivity  
Disorder (ADHD) effective plasma level in said patient for  
at least 8 hours without further administration of  
amphetamine base salts and which has a plasma  
10 concentration/time curve which is substantially the same as  
that of Figure 7, adjusted proportionally for said dosage  
amounts.

32. An oral pharmaceutical composition for delivery of  
one or more amphetamine base salts comprising an immediate  
15 release dosage form containing a first dosage amount of said  
one or more salts effective to treat Attention Deficit  
Hyperactivity Disorder (ADHD) in a human patient, and a  
second dosage form containing a second dosage amount of said  
one or more salts effective to treat ADHD in a human  
20 patient, wherein the plasma concentration/time profile of  
said composition is substantially the same as that of  
Figure 7, adjusted proportionally for said first and second  
dosage amounts.

33. The pharmaceutical composition of any one of  
25 claims 22 to 30 and 32, wherein said first and second dosage  
amounts are substantially equal.

34. An orally administrable pharmaceutical composition  
comprising:

(a) an immediate release dosage form containing a  
30 first dosage amount of one or more amphetamine base salts

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effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and

(b) a delayed release dosage form containing a second dosage amount effective to treat ADHD in a human patient of one or more amphetamine base salts,

wherein said amphetamine base salts are released from the delayed release dosage form beginning at a time after administration such that the maximum plasma concentration of the amphetamine base salts reaches a level greater than any previous level reached after the beginning of said immediate release, and

wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

35. A pharmaceutical composition of claim 34, wherein said first and second dosage amounts are substantially equal, wherein the amphetamine base salts are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, wherein said dosage forms each comprise core beads coated with said amphetamine base salts and said second dosage form further comprises a pH-dependent enteric matrix or coating, and wherein said beads are contained in a capsule.

36. An orally administrable pharmaceutical composition comprising:

(a) an immediate release dosage form containing a first dosage amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and

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(b) a delayed release dosage form containing a second dosage amount effective to treat ADHD in a human patient of one or more amphetamine base salts,

wherein said amphetamine base salts are released  
5 from the delayed release dosage form beginning at a time after administration such that the maximum plasma concentration of amphetamine is reached about 7 hours after administration,

wherein said composition is sufficient to maintain  
10 an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

37. The pharmaceutical composition of any one of claims 1 to 13, wherein the pharmaceutically active  
15 amphetamine salts are pharmaceutically active amphetamine base salts.

38. The pharmaceutical composition of any one of claims 14 to 30 and 32 to 37, wherein each of said first and second dosage amounts is about 10 mg of amphetamine base  
20 salts.

39. The pharmaceutical composition of any one of claims 14 to 30 and 32 to 37, wherein each of said first and second dosage amounts is about 5 mg of amphetamine base salts.

25 40. The pharmaceutical composition of any one of claims 14 to 30 and 32 to 37, wherein each of said first and second dosage amounts is about 20 mg of amphetamine base salts.



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41. The pharmaceutical composition of any one of claims 14 to 30 and 32 to 37, wherein each of said first and second dosage amounts is about 30 mg of amphetamine base salts.
- 5 42. The pharmaceutical composition of any one of claims 14 to 41, wherein the amphetamine base salts are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.
- 10 43. The pharmaceutical composition of any one of claims 14 to 41, wherein said amphetamine base salts are a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.
- 15 44. The pharmaceutical composition of any one of claims 14 to 43, wherein said amphetamine base salts consist essentially of d-amphetamine or consist essentially of l-amphetamine.
- 20 45. The pharmaceutical composition of any one of claims 14 to 43, wherein said amphetamine base salts are a salt of dl-amphetamine.
- 25 46. The pharmaceutical composition of any one of claims 22 to 45 sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.
- 30 47. The pharmaceutical composition of any one of claims 22 to 45 sufficient to maintain an effective level of amphetamine base salts in the patient over the course of 12 hours without further administration of amphetamine base salts.

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48. The pharmaceutical composition of any one of claims 22 to 45, sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts, wherein said first and second dosage amounts are substantially equal, wherein the amphetamine base salts are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, wherein said dosage forms each comprise core beads coated with said amphetamine base salts and said second dosage form further comprises a pH-dependent enteric matrix or coating, and wherein said beads are contained in a capsule.

49. The pharmaceutical composition of any one of claims 1 to 13 sufficient to maintain an effective level of amphetamine salts in the patient over the course of at least 8 hours without further administration of amphetamine salt.

50. The pharmaceutical composition of any one of claims 1 to 13 sufficient to maintain an effective level of amphetamine salts in the patient over the course of 12 hours without further administration of amphetamine salt.

51. An orally administrable pharmaceutical composition comprising:

(a) an immediate release dosage form containing an amount of one or more amphetamine base salts effective to treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and

(b) a delayed release dosage form containing an amount effective to treat ADHD in a human patient of one or more amphetamine base salts,

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wherein said salts are a mixture of  
dextroamphetamine sulfate, dextroamphetamine saccharate,  
amphetamine aspartate monohydrate and amphetamine sulfate,

wherein said amphetamine base salts are released  
5 from the delayed release dosage form beginning at a time  
after administration such that the maximum plasma  
concentration of dextro-salts in said mixture is about 40  
ng/ml for about a 10 mg dose in each of said dosage forms,  
or a concentration proportional thereto for a dose in each  
10 of said dosage forms other than about 10 mg, and

wherein said composition is sufficient to maintain  
an effective level of amphetamine base salts in the patient  
over the course of at least 8 hours without further  
administration of amphetamine base salts.

15 52. An orally administrable pharmaceutical composition  
comprising amphetamine base salts, which has substantially  
the same mean plasma concentration profile as an orally  
administrable pharmaceutical composition comprising:

(a) an immediate release dosage form containing an  
20 amount of one or more amphetamine base salts effective to  
treat Attention Deficit Hyperactivity Disorder (ADHD) in a  
human patient coated onto a particulate core; and

(b) a delayed release dosage form containing  
substantially the same amount effective to treat ADHD in a  
25 human patient of one or more amphetamine base salts, coated  
onto a particulate core and having thereon a pH-dependent  
enteric coating comprising a copolymer of methacrylic acid  
and methacrylic acid methyl ester,

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wherein said salts are a mixture of  
dextroamphetamine sulfate, dextroamphetamine saccharate,  
amphetamine aspartate monohydrate and amphetamine sulfate,

wherein essentially all of said amphetamine base  
5 salts are released from the delayed release dosage form  
within about 60 minutes after initiation of said delayed  
release, beginning at a time after administration such that  
the maximum plasma concentration of the amphetamine base  
salts reaches a level greater than any previous level  
10 reached after the beginning of said immediate release, and

wherein said composition is sufficient to maintain  
an effective level of amphetamine base salts in the patient  
over the course of at least 8 hours without further  
administration of amphetamine base salts,

15 said composition having said substantially the  
same mean plasma concentration profile.

53. An orally administrable pharmaceutical composition  
comprising:

(a) an immediate release dosage form containing an  
20 amount of a mixture of amphetamine base salts effective to  
treat Attention Deficit Hyperactivity Disorder (ADHD) in a  
human patient; and

(b) a delayed release dosage form containing an  
amount effective to treat ADHD in a human patient of a  
25 mixture of amphetamine base salts,

wherein said delayed release dosage form comprises  
amphetamine base salts coated with a pH-dependent enteric  
matrix or coating of a thickness of equal to or greater than  
about 20  $\mu\text{m}$ , and

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wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

5 54. The pharmaceutical composition of claim 53 wherein said thickness is equal to or greater than about 25  $\mu$ m.

55. The pharmaceutical composition of claim 53 or 54 wherein said amphetamine base salts are a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate,  
10 amphetamine aspartate monohydrate and amphetamine sulfate.

56. The pharmaceutical composition of claim 55 wherein said pH-dependent enteric coating or matrix comprises cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate  
15 phthalate, carboxymethylethylcellulose, or copolymerized methacrylic acid/methacrylic acid methyl ester.

57. The pharmaceutical composition of claim 56 wherein said amphetamine base salts are released from the delayed release dosage form beginning at a time after administration  
20 such that the maximum plasma concentration of the amphetamine base salts reaches a level greater than any previous level reached after the beginning of said immediate release.

58. The pharmaceutical composition of claim 55 wherein  
25 said pH-dependent enteric coating or matrix comprises copolymerized methacrylic acid/methacrylic acid methyl ester.

59. The pharmaceutical composition of claim 55 wherein said amphetamine base salts are released from the delayed  
30 release dosage form beginning at a time after administration

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such that the maximum plasma concentration of the amphetamine base salts reaches a level greater than any previous level reached after the beginning of said immediate release.

5 60. The pharmaceutical composition of any one of claims 55 to 59 wherein the plasma concentration profile has only one two-sided peak.

61. The pharmaceutical composition of any one of claims 55 to 59 wherein the plasma concentration profile has  
10 two two-sided peaks.

62. An orally administrable pharmaceutical composition comprising:

(a) an immediate release dosage form containing an amount of a mixture of amphetamine base salts effective to  
15 treat Attention Deficit Hyperactivity Disorder (ADHD) in a human patient; and

(b) a delayed release dosage form containing an amount effective to treat ADHD in a human patient of a mixture of amphetamine base salts,

20 wherein said mixture of amphetamine base salts comprises dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate,

wherein said delayed release dosage form comprises  
25 amphetamine base salts coated with a pH-dependent enteric matrix or coating of a thickness of equal to or greater than about 20  $\mu\text{m}$ ,

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wherein said pH-dependent matrix or coating comprises copolymerized methacrylic acid/methacrylic acid methyl ester, and

5 wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salts.

63. Use of a pharmaceutical composition of any one of claims 1 to 62 for treating Attention Deficit Hyperactivity  
10 Disorder (ADHD).

64. A kit comprising a pharmaceutical composition of any one of claims 1 to 62 together with instructions for treating Attention Deficit Hyperactivity Disorder (ADHD).

65. A dosage form for once a day administration of one  
15 or more amphetamine base salts, produced by a process comprising,

coating first particulate cores with said amphetamine base salts to provide immediate release of said salts upon administration,

20 coating second particulate cores with one or more amphetamine base salts and then coating the resultant amphetamine base salts coated cores with an enteric coating effective to delay the onset of release of said amphetamine base salts such that the maximum plasma concentration of the  
25 amphetamine base salts reaches a level greater than any previous level reached after the beginning of said immediate release,

drying said coated cores, and

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filling a dosage form with a sufficient amount of each of said first and second coated cores such that said dosage form is sufficient to maintain an effective level of amphetamine base salts in a patient over the course of at  
5 least 8 hours without further administration of amphetamine base salts.

66. The dosage form of claim 65 wherein the amphetamine base salts are a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate  
10 monohydrate and amphetamine sulfate.

67. The dosage form of claim 66 wherein said enteric coating is a copolymer of methacrylic acid and methacrylic acid methyl ester.

68. The dosage form of claim 66 wherein said enteric  
15 release coating releases essentially all of said amphetamine base salts coated on said second cores within about 60 minutes after initiation of release from said second cores.

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FIG. 1

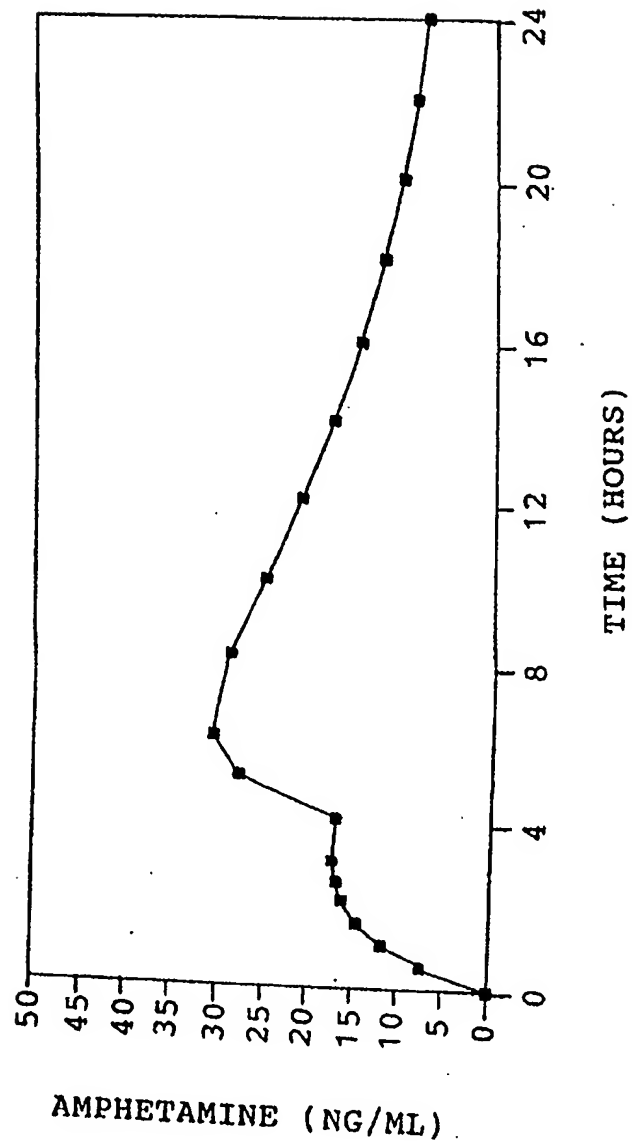


FIG. 2A

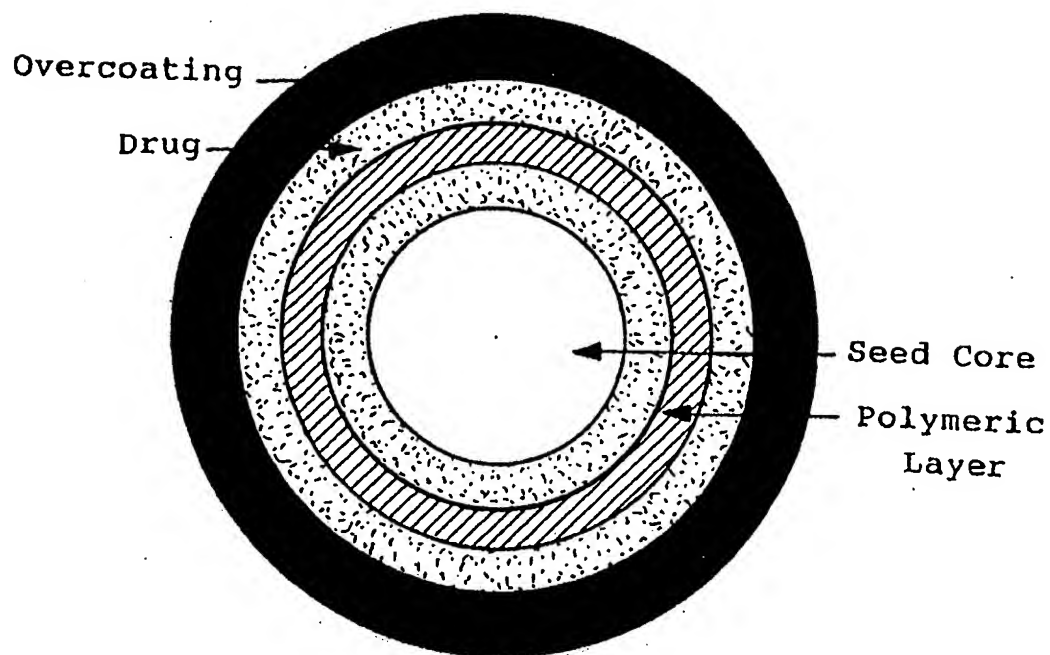


FIG. 2B

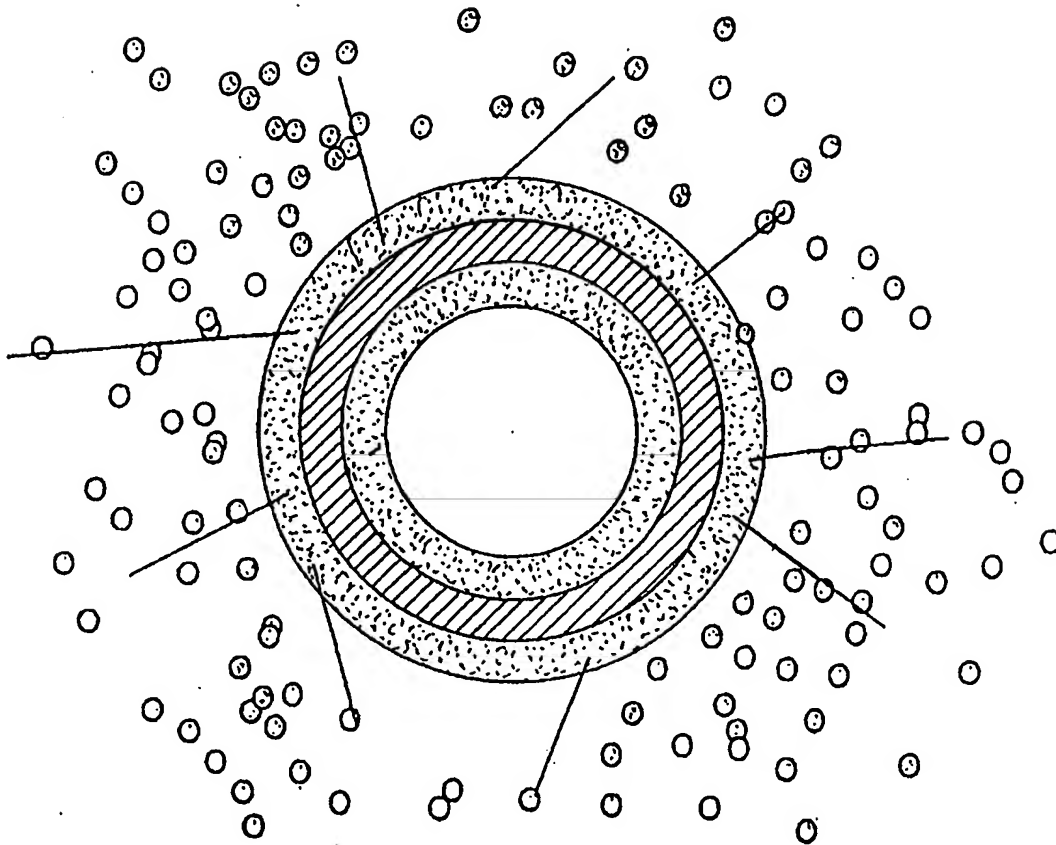
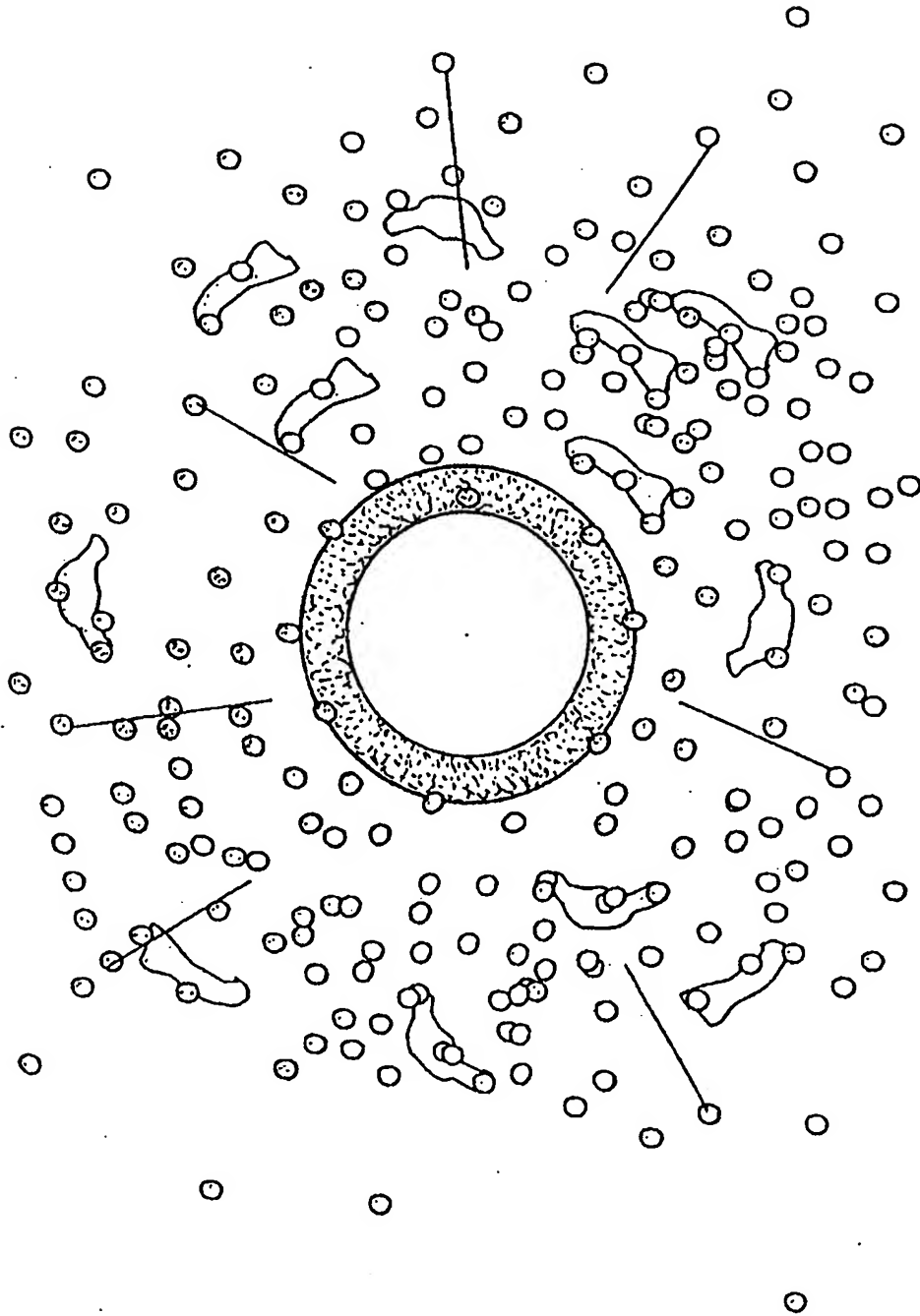


FIG. 2C



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FIG. 3

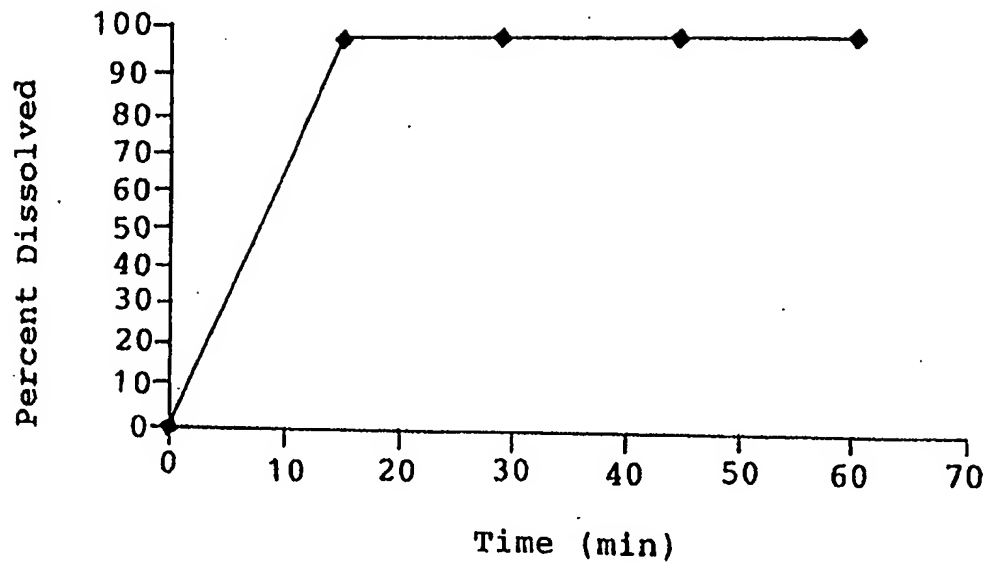
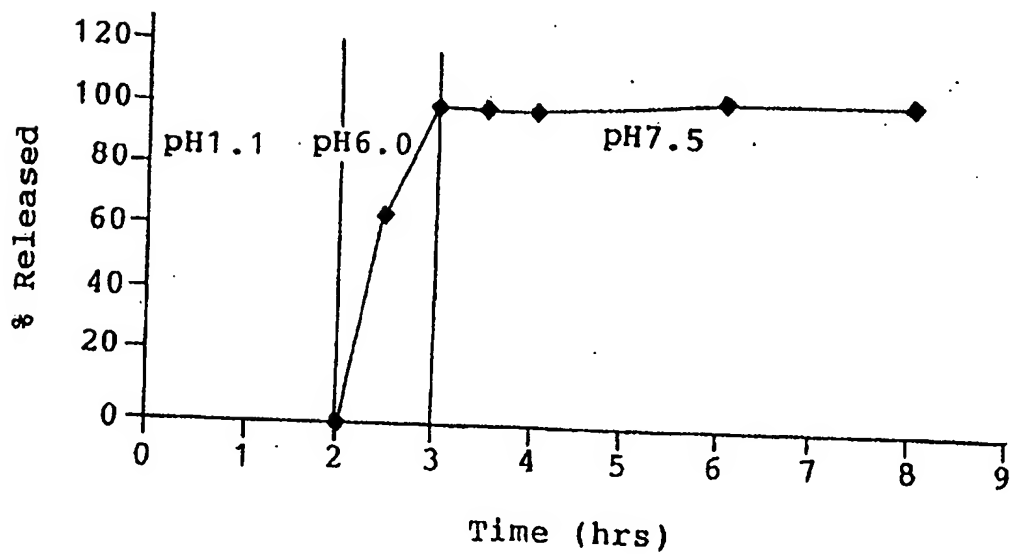


FIG. 4



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FIG. 5

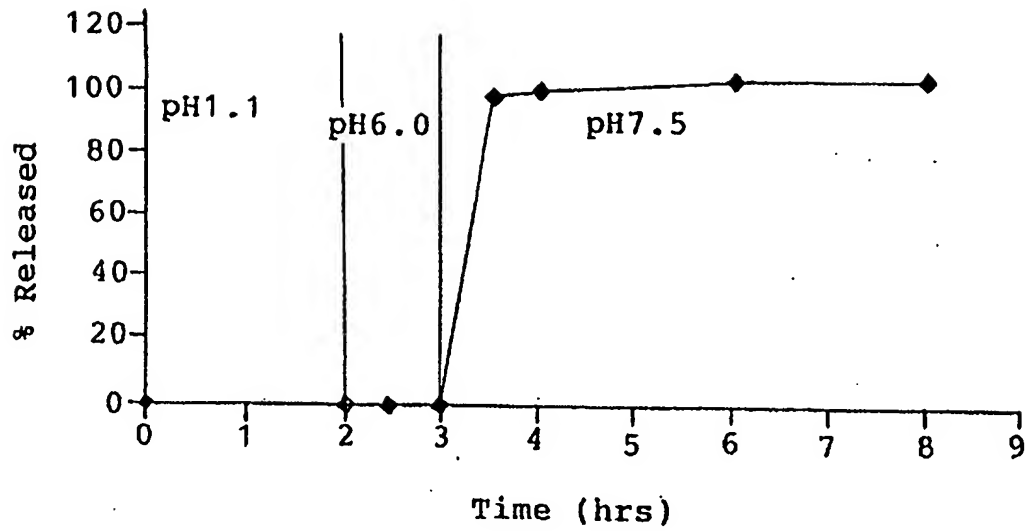
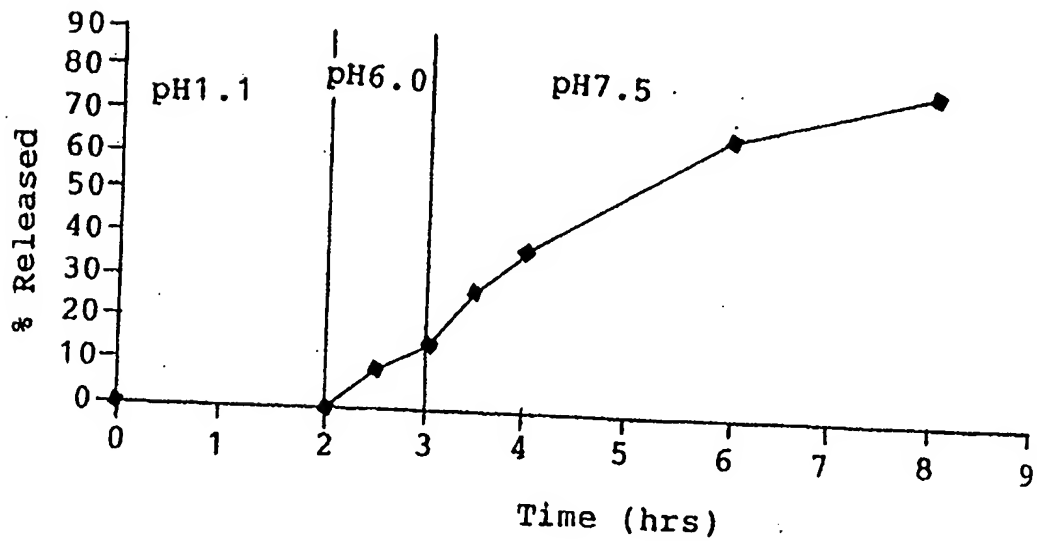


FIG. 6



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FIG. 7

Dataset subject 3 phase 4 (Extravascular)

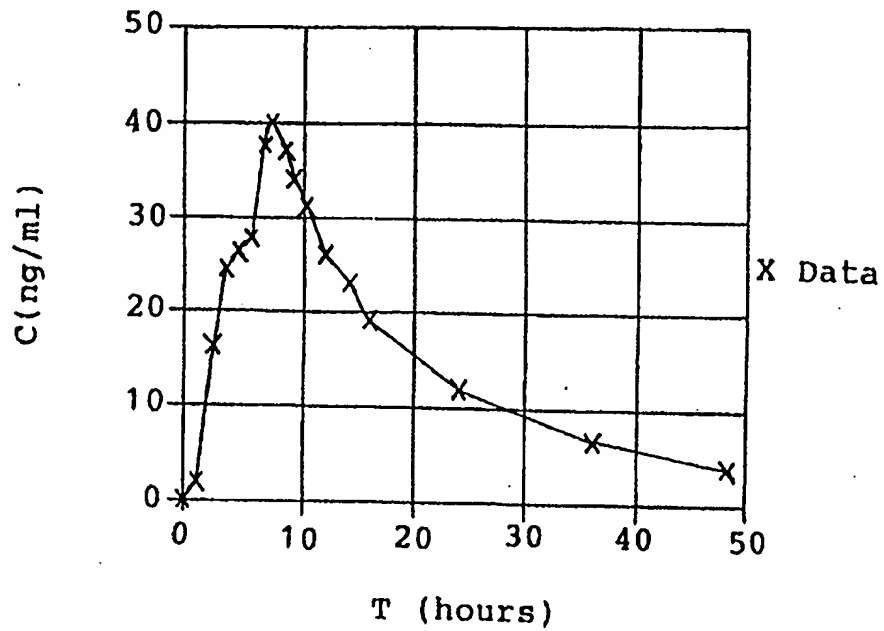


FIG. 8

Dataset subject 18 phase 2 (Extravascular)

